Single-Pill Combination Regimens for Treatment of HIV-1 Infection

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This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the authors’ clinical recommendations.

A 52-year-old man with a history of homelessness, depression, and polysubstance use received a diagnosis of human immunodeficiency virus type 1 (HIV-1) infection in 2005 but has declined antiretroviral therapy (ART) in the past. His CD4+ T-cell count is now 257 per cubic millimeter, and his plasma HIV-1 RNA level is 17,000 copies per milliliter. The patient was prescribed a multipill antiretroviral regimen 2 months ago but has not followed this regimen regularly because “taking out lots of pills in the shelter just announces to the world that I have AIDS [the acquired immunodeficiency syndrome].” The patient desires to keep his HIV status private and states that he would take medications regularly if he could take just “one pill once a day.” The patient is not taking any other medications; his renal function is normal. How should he be evaluated and treated?

The Clinical Problem

Effective HIV treatment requires lifelong and daily consumption of multiple antiretroviral medications. With the advent and refinement of combination ART, the life expectancy of HIV-infected patients has risen dramatically. In addition to benefiting infected persons, ART almost completely blocks HIV-1 transmission to uninfected sexual partners. If we were able to treat most or all HIV-infected patients and thereby prevent new infections, “the beginning of the end of AIDS” would be in sight.

For the benefits of ART to be realized at the individual and population levels, patients must maintain high levels of adherence to all components of the regimen. A number of factors are associated with lower levels of adherence, including the stigma associated with HIV infection, membership in a minority racial or ethnic group, alcohol or drug use, cognitive impairment, young age, and medication side effects. Moreover, rates of adherence to ART may decline over time, even when antiretroviral agents are provided at no cost. There is therefore a compelling need for strategies that can help patients sustain lifelong adherence to treatment.

When effective ART was first developed almost two decades ago, adherence was particularly challenging because patients had to consume handfuls of pills, often with substantial toxicity, multiple times per day. With the introduction of coformulated drugs that are less toxic and more potent, there have been dramatic reductions in the pill burden. This trend has culminated in single-pill combinations, in which all components of an ART regimen, typically three or more medications from two different drug classes, are formulated into one pill taken once daily.
BIOLGIC FEATURES OF HIV-1 INFECTION

The rationale for lifelong combination therapy for HIV-1 infection and the interest in developing single-pill combinations to facilitate adherence are based on the biologic features of the virus (Fig. 1). Because of the high replication and mutation rates of HIV-1, multiple antiretroviral agents (usually three) must be taken simultaneously to suppress replication and prevent the development of viral resistance. ART can reduce HIV-1 RNA to extremely low levels in the blood, although the virus still persists in reservoirs found in specialized immune cells and tissues.21 Because antiretroviral regimens typically cannot eradicate infection, even when additional agents are added,22-23 therapy must be continued over a lifetime to suppress viral replication and prevent HIV-related complications.

Owing to the ability of HIV-1 to mutate rapidly, the effect of suboptimal adherence to ART can be devastating (Fig. 2). Incomplete adherence leads to ongoing HIV-1 replication, which, in the presence of low-to-moderate levels of drug exposure, can select for viral strains with mutations conferring resistance to those agents. The rapidity with which drug-resistant strains emerge and the subsequent immunologic and clinical consequences vary according to the HIV-1 RNA level, the antiretroviral class, and the fitness of the mutant virus. At the individual level, inconsistent adherence can lead to drug resistance, permanently rendering particular agents or classes of drugs ineffective.24 At the population level, inconsistent use of antiretroviral agents can lead to ongoing transmission and spread of drug-resistant viral strains. Regimens with a low pill burden, such as single-pill combinations, may both facilitate adherence over a prolonged period and ensure that none of the components of a combination regimen are inadvertently missed.

CLINICAL EVIDENCE

There are currently three single-pill combinations marketed for HIV-1 treatment, each containing the same combination of one nucleotide reverse transcriptase inhibitor and one nucleoside reverse transcriptase inhibitor (NRTIs): tenofovir disoproxil fumarate (TDF) at a dose of 300 mg and emtricitabine (FTC) at a dose of 200 mg, respectively. The first agent (Atripla, Bristol-Myers Squibb and Gilead Sciences), released in 2006, is a single pill that combines TDF–FTC with 600 mg of the nonnucleoside reverse transcriptase inhibitor (NNRTI) efavirenz (EFV). The second agent (Complera, Gilead Sciences), approved in 2011, combines TDF–FTC with 25 mg of the NNRTI rilpivirine (RPV). The third agent (Stribild, Gilead Sciences), released in 2012, consists of TDF–FTC combined with 150 mg of the integrase strand transfer inhibitor (INSTI) elvitegravir (EVG) and 150 mg of the pharmacoenhancer cobicistat (which boosts serum EVG levels). A fourth single-pill combination is in development and has not yet been approved for clinical use. This agent would combine two NRTIs — abacavir (ABC) at a dose of 600 mg and lamivudine (3TC) at a dose of 300 mg — with 50 mg of the recently approved INSTI dolutegravir (DTG).

Studies of once-daily dosing of antiretroviral agents provide support for the concept that regimen simplification improves adherence. One meta-analysis examined adherence among patients with HIV-1 infection who received either once-daily or twice-daily regimens in 19 randomized, controlled studies (6321 patients).20 Modestly better adherence, assessed by means of pill counts or medication-event monitoring systems, was observed among recipients of once-daily regimens (an increase of 2.55 percentage points, P<0.001), although there were no overall differences in the virologic-suppression rate between the two groups.20 Regimens involving fewer numbers of pills improved both rates of adherence and virologic suppression.20

The effect of single-pill combinations on adherence and outcomes has been assessed by comparing patients receiving the EFV–TDF–FTC single-pill combination agent with those taking multipill combinations. The only published randomized trial to make this comparison enrolled 300 patients receiving stable ART and assigned them either to continue their previous regimen or to switch to EFV–TDF–FTC as a single pill.25,26 At 48 weeks, patient-reported treatment adherence was 96% or higher in both groups, and the rate of virologic suppression did not differ significantly between the two groups;25 91% of participants, however, stated their preference for the EFV–TDF–FTC regimen.26 In an open-label prospective study using within-patient analyses, 202 patients receiving stable two- or three-drug EFV-based ART were switched to the single-pill combination of EFV–TDF–FTC27; the adherence rate increased from
93.8% to 96.1% (P<0.01), with improvements in self-reported quality of life. These two studies probably underestimate the benefit of single-pill combinations because most participants were already receiving a stable ART regimen, with virologic suppression, before making the switch.25,27 Several observational studies, including a prospective analysis in a cohort of homeless and
marginally housed patients,28 have also shown higher rates of adherence or improved outcomes with single-pill combinations.29-32 For example, a retrospective analysis compared rates of adherence (measured on the basis of pharmacy refill data) among approximately 7000 patients receiving ART composed of one, two, or three or more pills per day.30 Adherence of 95% or higher was more likely with a single-pill combination than with a regimen of three or more pills per day.30 Similar findings were seen in observational studies involving HIV-infected Medicaid enrollees,31 U.S. veterans,32 and an Italian cohort,29 although confounding by indication may play a role in all these observational results.

Clinical Use

ART is usually initiated as a regimen consisting of two NRTIs (the “backbone”) combined with a third agent (the “anchor”), which consists of an NNRTI, a protease inhibitor boosted with a pharmacoenhancer, or an INSTI. There are a number of considerations in the choice of a regimen, including drug resistance (as assessed by means of HIV-1 genotyping), potential adverse drug effects, drug–drug interactions, food restrictions, convenience, and cost.

Selection of a Single-Pill Combination Regimen

Several additional factors must be weighed in deciding on the use of a single-pill combination (Fig. 3 and Table 1). These include determination of which NRTI combination (TDF–FTC or ABC–3TC) is appropriate and whether a protease inhibitor (not included in any of the currently available combinations) is preferable in the regimen. Single-pill combinations should be avoided in patients with clinically significant renal disease because TDF, 3TC, and FTC all require dose reductions or elimination when the estimated creatinine clearance is less than 50 ml per minute. The inability to adjust the dose of individual drug components in patients with renal insufficiency is an important limitation of single-pill combinations. In addition, patients who have drug-resistant HIV-1 infection often require agents that are not included in single-pill combinations.

Selection of an NRTI Backbone

The two most commonly used NRTI combinations in the United States are TDF–FTC and ABC–3TC. Both are available as fixed-dose formulations, but only TDF–FTC is currently available in single-pill combination regimens. Selection of the NRTI combination is mainly driven by a choice between TDF and ABC because both FTC and 3TC have relatively few adverse effects. TDF–FTC has excellent potency and durable effectiveness, but TDF can trigger proximal tubulopathy or frank renal insufficiency, particularly in patients with risk factors for kidney disease and those taking protease inhibitors.33,34 Patients receiving TDF-containing regimens also have a larger drop in bone mineral density after ART initiation than those receiving ABC-containing regimens,35,36 although changes in bone density subsequently stabilize. Use of ABC–3TC requires initial testing of the patient for HLA B5701, a genetic polymorphism that is present in approximately 8% of whites and 2.5% of blacks in the United States37 and that predicts ABC-related
hypersensitivity.\textsuperscript{38} When combined with EFV or ritonavir-boosted atazanavir, ABC–3TC resulted in inferior virologic responses as compared with responses observed with TDF–FTC in patients with pretherapy HIV-1 RNA levels of 100,000 copies per milliliter or higher\textsuperscript{39,46}; this difference was not observed when the HIV-1 RNA level was less than 100,000 copies per milliliter or when ABC–3TC was combined with other agents (e.g., DTG).\textsuperscript{41-44} Although some clinicians avoid the use of ABC in patients who are at high risk for cardiovascular disease because of a putative link between the drug and myocardial infarction, this finding is controversial\textsuperscript{45} and has not been confirmed in other studies, including a meta-analysis conducted by the Food and Drug Administration (FDA).\textsuperscript{46}

\textbf{SELECTION OF AN ANCHOR DRUG}

None of the current single-pill combinations contain protease inhibitors, which should be used in patients with known viral resistance to NNRTIs or INSTIs. In addition, because transmitted resistance to protease inhibitors is uncommon and resistance to this class emerges relatively slowly, protease inhibitors are often favored when treatment decisions are required before resistance-testing results are available — for example, in the case of patients with acute HIV-1 infection\textsuperscript{19} or opportunistic infections.\textsuperscript{47} Protease inhibitors are also sometimes considered in patients with inconsistent adherence because multiple viral mutations are required to compromise the activity of these agents. Disadvantages of regimens containing protease inhibitors include higher pill burdens (typically three pills per day) and drug interactions due to inhibition of the cytochrome P-450 3A4 (CYP3A4) enzyme system by these agents.

The anchor drug raltegravir does not inhibit CYP3A4 activity and has few drug–drug interactions, with excellent virologic activity.\textsuperscript{48} Like other INSTIs, raltegravir should not be administered with antacids that contain divalent cations; these agents can reduce INSTI absorption through chelation. However, unlike other recommended anchors, all with once-daily dosing, raltegravir requires twice-daily dosing\textsuperscript{49} and is therefore not available in a single-pill combination.

EFV, the anchor drug in EFV–TDF–FTC, is potent and, in recent years, the drug to which every newly developed anchor antiretroviral agent has been compared. EFV may cause neuropsychiatric effects (e.g., vivid dreams, insomnia, somnolence, and depression) or rash, although symptoms typically diminish over time. The FDA has cate-

\begin{figure}[h]
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\includegraphics[width=\textwidth]{image3.png}
\caption{Factors to Consider in the Use of a Single-Pill Combination (SPC) for the Treatment of HIV Infection.}
\end{figure}

For patients who require a protease inhibitor–based regimen, no combination containing a protease inhibitor is currently available as a single pill. In addition, no combination formulated as a single pill is appropriate for patients with an estimated creatinine clearance of less than 50 ml per minute, because the NNRTIs (lamivudine [3TC], emtricitabine [FTC], and tenofovir disoproxil fumarate [TDF]) that are incorporated into single-pill formulations require dose adjustments in such patients. In the absence of these constraints, combination therapy administered as a single-pill formulation may be a suitable option. For patients who are positive for HLA B5701 as determined by host genetic testing, the combination of dolutegravir (DTG), abacavir (ABC), and 3TC should not be used. For patients with an HIV-1 RNA level of 100,000 copies per milliliter or less, any of the single-pill combination regimens may be used. For those with an HIV-1 RNA level of more than 100,000 copies per milliliter or with a CD4+ T-cell count of 200 per cubic millimeter or less, the combination of rilpivirine (RPV), TDF, and FTC should not be used. For patients with a creatinine clearance of less than 70 ml per minute, the combination of elvitegravir (EVG), cobicistat, TDF, and FTC should not be initiated. The DTG–ABC–3TC combination has not yet been approved as a single pill for clinical use.
gorized EFV as a class D agent with respect to pregnancy risk on the basis of data from primate models, although the extent of teratogenicity in humans is unclear.\textsuperscript{50–52} According to U.S. guidelines, EFV should be avoided in sexually active women of reproductive potential who are not using contraception, although discontinuing EFV if pregnancy occurs is not recommended and EFV is the preferred NNRTI during pregnancy, when initiated 8 weeks after conception.\textsuperscript{53} The World Health Organization (WHO) recommends EFV as a first-line agent for women regardless of reproductive potential or pregnancy.\textsuperscript{54} Finally, EFV can cause dyslipidemia, although it has not been linked to an increased rate of myocardial infarction.\textsuperscript{55}

RPV, the anchor drug in RPV–TDF–FTC, was approved on the basis of double-blind, double-dummy trials comparing it with EFV, each in combination with TDF–FTC\textsuperscript{56} or investigator-selected NRTIs.\textsuperscript{57} The pooled 96-week analysis of these studies showed equal rates of virologic suppression in the RPV and EFV groups.\textsuperscript{58} The RPV group had fewer treatment discontinuations due to adverse events and lower rates of rash, central nervous system effects, and adverse lipid effects than the EFV group. Among patients whose pretherapy HIV-1 RNA level was more than 100,000 copies per milliliter or whose CD4+ T-cell count was less than 200 per cubic millimeter, however, virologic-failure rates were higher with RPV. Moreover, among patients with virologic failure, HIV-1 drug resistance mutations emerged more frequently in patients receiving RPV. In an open-label, randomized study comparing RPV–TDF–FTC with EFV–TDF–FTC, each administered as a single-pill combination,\textsuperscript{59} RPV was superior to EFV in patients with pretherapy HIV-1 RNA levels of 100,000 copies per milliliter or less and was noninferior to EFV in patients with HIV-1 RNA levels of more than 100,000 copies per milliliter; in patients with viral loads of more than 500,000 copies per milliliter, the rate of virologic failure in the RPV group was higher. RPV-based regimens are not recommended for patients whose pretherapy HIV-1 RNA level is more than 100,000 copies per milliliter or whose CD4+ T-cell count is 200 per cubic millimeter or less.\textsuperscript{59} RPV must be taken with a solid meal (≥390 kcal)\textsuperscript{60} and requires stomach acid for adequate absorption, precluding the concomitant use of proton-pump inhibitors. In addition to its use in initial therapy, RPV–TDF–FTC may have a role in patients with virologic suppression during treatment with a protease inhibitor–containing regimen who have a reason to change medications: in a recent trial, switching such patients to RPV–TDF–FTC maintained high rates of virologic suppression and improved lipid levels.\textsuperscript{61}

EVG, together with the pharmacoenhancer cobicistat, is the anchor drug in the single-pill combination EVG–cobicistat–TDF–FTC. This combination was noninferior to two other first-line regimens, TDF–FTC with either EFV\textsuperscript{62–64} or ritonavir-boosted atazanavir.\textsuperscript{65} In the STRATEGY trials, patients with virologic suppression who were switched from an NNRTI-containing or protease inhibitor–containing regimen to EVG–cobicistat–TDF–FTC continued to have high rates of virologic suppression.\textsuperscript{66,67} Cobicistat-boosted EVG does not have neuropsychiatric effects and does not commonly cause rash. However, cobicistat inhibits tubular secretion of creatinine without reducing the creatinine clearance. As a result, patients may have a mild increase in the serum creatinine level, typically less than 0.4 mg per deciliter (35 μmol per liter), with this medication initially; if a higher elevation occurs, evaluation for TDF-induced damage is warranted. The studies that led to drug approval involved patients with an estimated creatinine clearance of more than 70 ml per minute, so use should be limited to this group.\textsuperscript{59} Cobicistat is a potent CYP3A4 inhibitor with potential drug–drug interactions.

DTG is a recently approved INSTI; the recommended dose in previously untreated patients and in previously treated patients who did not receive an INSTI is 50 mg once daily, allowing its potential use in a single-pill combination. Three randomized, phase 3 trials have compared DTG with other first-line agents in previously untreated patients. In the SPRING-2 study, DTG was noninferior to raltegravir when combined with either TDF–FTC or ABC–3TC.\textsuperscript{42–43} In the SINGLE study, DTG was superior to EFV–TDF–FTC,\textsuperscript{58} largely because of more treatment-related discontinuations with EVF. In the FLAMINGO study, DTG was superior to ritonavir-boosted darunavir with either TDF–FTC or ABC–3TC,\textsuperscript{44} in part because of higher rates of study withdrawal in the darunavir group and lower rates of virologic nonresponse among patients in the DTG group who had high viral loads at baseline. DTG was also superior to raltegravir, each given with other agents, in previously treated patients who had...
not received an INSTI, and it retains activity against some raltegravir-resistant viruses when given twice daily. A single-pill combination containing DTG–ABC–3TC is pharmacokinetically bioequivalent to the individual components of DTG plus ABC–3TC, and an application for approval of the single-pill formulation is under review at the FDA. DTG, like protease inhibitors, appears to have a high genetic barrier to resistance, which could help prevent the development of resistance in patients with inconsistent adherence; however, more clinical experience is needed to assess the role of DTG in this context.

Table 1. Considerations for the Use of Particular Single-Pill Combinations in the Management of HIV-1 Infection.†

<table>
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<tr>
<th>Single-Pill Combination</th>
<th>Pros</th>
<th>Cons and Other Considerations</th>
<th>Average Wholesale Price per Month</th>
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<tr>
<td>EFV–TDF–FTC (Atripla)</td>
<td>This combination has the longest record of safety and effectiveness. TDF and FTC have activity against HBV; regimens containing both drugs are recommended for patients with HIV–HBV coinfection.</td>
<td>EFV is potentially teratogenic; avoid in women trying to conceive, although it can be continued in pregnant women with virologic suppression who present for antenatal care in the first trimester. EFV may cause neuropsychiatric effects; avoid in patients with psychosis or depression. EFV raises lipid levels, and it may cause rash, typically mild to moderate in severity and rarely requiring discontinuation. To ameliorate neuropsychiatric effects, the combination is often given at bedtime. It should be taken on an empty stomach, since food increases absorption, which may increase the risk of adverse effects.</td>
<td>$2,402.04</td>
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<tr>
<td>RPV–TDF–FTC (Complera)</td>
<td>As compared with EFV, RPV is associated with lower rates of neuropsychiatric events and rash and has more favorable lipid effects. Patients with virologic suppression during treatment with a protease inhibitor–based regimen who switch to RPV–TDF–FTC have a high rate of continued virologic suppression and improved lipid levels. RPV is not known to be teratogenic in humans (pregnancy class B). TDF and FTC have activity against HBV; regimens containing both drugs are recommended for patients with HIV–HBV coinfection.</td>
<td>This combination is not recommended if pretherapy HIV-1 RNA level is &gt;100,000 copies/ml or if CD4+ T-cell count is ≤200/mm³. RPV must be taken with a meal (≥390 kcal); administration with a protein shake decreases absorption. RPV requires acid for absorption. Do not use proton-pump inhibitors; use antacids and H₂-receptor antagonists with caution. Use caution if patient is taking another drug that has been associated with prolongation of the QTc interval.</td>
<td>$2,463.37</td>
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<tr>
<td>EVG–cobicistat–TDF–FTC (Stribild)</td>
<td>EVG–cobicistat does not cause the neuropsychiatric effects or rash observed with EFV, and it has more favorable lipid effects than EFV. Patients with virologic suppression during treatment with a protease inhibitor–based or NNRTI–based regimen who switch to EVG–cobicistat–TDF–FTC have a high rate of continued virologic suppression. EVG–cobicistat is not known to be teratogenic in humans (pregnancy class B). TDF and FTC have activity against HBV; regimens containing both drugs are recommended for patients with HIV–HBV coinfection.</td>
<td>Cobicistat inhibits tubular secretion of creatinine, leading to an early modest increase in the serum creatinine level in some patients (average increase, 0.14 mg/dl; increase is usually &lt;0.4 mg/dl). The increase is usually reversible with treatment discontinuation. This combination is not currently recommended for patients with mild or moderate renal insufficiency. (Studies to date involved patients with an estimated creatinine clearance of &gt;70 ml/min.) EVG is not active against viral strains that are resistant to raltegravir (an important consideration for use in second-line regimens). As a CYP3A4 inhibitor, cobicistat can affect the metabolism of commonly used medications, such as statins (lovastatin and simvastatin are contraindicated), rifampin (particularly important in HIV–tuberculosis coinfection), phosphodiesterase type 5 inhibitors (e.g., sildenafil), and fluticasone. This combination should be taken with food and should be administered at least 2 hr before or after magnesium-containing, aluminum-containing, or calcium carbonate antacids.</td>
<td>$2,948.70</td>
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Areas of Uncertainty

The potential benefits of single-pill combinations must be weighed against the higher costs of these branded combinations as compared with multipill regimens containing generic antiretroviral agents. One analysis projected that switching patients with HIV-1 infection from the branded EFV–TDF–FTC single-pill combination to a three-pill regimen of generic EFV (not yet available), branded TDF, and generic 3TC would save almost $1 billion per year in the United States, with a relatively small reduction in treatment efficacy.\(^7\) A study from Denmark showed that switching patients from a branded single-pill combination to a cheaper multipill regimen did not compromise virologic efficacy.\(^8\) In patients who struggle with adherence, however, the decreased pill burden of a single-pill combina-

### Table 1. (Continued.)

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<th>Single-Pill Combination</th>
<th>Pros</th>
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<td><strong>Pending FDA approval</strong></td>
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<tr>
<td>DTG–ABC–3TC</td>
<td>In phase 3 trials involving previously untreated patients, DTG-based regimens were superior to EFV-based regimens and ritonavir-boosted, darunavir-based regimens and were noninferior to raltegravir-based regimens. In previously treated patients without INSTI resistance, DTG was superior to raltegravir with respect to virologic activity. DTG has few drug interactions. DTG can be taken with or without food. The ABC–3TC backbone can be used in patients with mild renal insufficiency (estimated creatinine clearance &gt;50 ml/min). DTG has had a high genetic barrier to resistance in trials to date. DTG is not known to be teratogenic in humans (pregnancy class B).</td>
<td>DTG inhibits creatinine secretion, leading to a small rise in the serum creatinine level in some patients (mean increase at 48 wk, 0.1 mg/dl [range, −0.6 to 0.6]) — an increase similar to that observed with cobicistat. Use of ABC-containing regimens requires genetic testing for HLA B5701, an allele that predicts hypersensitivity to this drug. DTG should be taken at least 2 hr before or 6 hr after oral administration of sucralfate or cation-containing antacids or laxatives with magnesium or aluminum; calcium or iron supplements can be administered with DTG with food (otherwise, DTG should be taken at least 2 hr before or 6 hr after the supplement is taken). Double the dose with concomitant rifampin or EFV; do not use with etravirine unless boosted protease inhibitors are being administered. No dose adjustments are needed with RPV. There is limited clinical experience with DTG to date (approved in August 2013). Some studies have shown a link between ABC and myocardial infarction, but there was no such relationship in other studies and an FDA meta-analysis.</td>
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<td><strong>In development for HIV-1 infection</strong></td>
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<td>EVG–cobicistat–TAF–FTC</td>
<td>Data to 48 wk suggest TAF may be associated with smaller reductions in bone density and estimated creatinine clearance than TDF. Available data are from a phase 2 study; no data beyond 48 wk are available. More information is needed.</td>
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\(^*\) ABC denotes abacavir, DTG dolutegravir, EFV efavirenz, EVG elvitegravir, FDA Food and Drug Administration, FTC emtricitabine, HBV hepatitis B virus, HIV human immunodeficiency virus, INSTI integrase strand-transfer inhibitor, NNRTI nonnucleoside reverse-transcriptase inhibitor, QTc corrected QT, RPV rilpivirine, TAF tenofovir alafenamide, TDF tenofovir disoproxil fumarate, and 3TC lamivudine.

**Agents in Development for Use in Single-Pill Combinations**

Tenofovir alafenamide (TAF), a prodrug of tenofovir that is converted to the active form in lymphocytes, is an agent being developed for use in single-pill combinations. The virologic activity of TAF was similar to that of TDF when each was coformulated with cobicistat–EVG–FTC and taken for 48 weeks.\(^4\) The TAF-containing regimen caused a smaller decline in bone mineral density and estimated creatinine clearance than the TDF-containing combination. Further studies of TAF-containing single-pill combinations, including ones that include protease inhibitors, are under way. Applications for the fixed-dose combinations of atazanavir–cobicistat\(^5\) and darunavir–cobicistat\(^7\) are under review at the FDA, and a single-pill combination regimen of darunavir–cobicistat–TAF–FTC is being studied in clinical trials.
tion could be crucial for successful treatment. Moreover, if a multipill regimen requires multiple copayments, the cumulative cost may be prohibitive for some patients. On a global scale, country- and region-specific pharmacoeconomic analyses are needed for single-pill combinations and other formulations (e.g., long-acting agents) designed to improve adherence.

**Guidelines**

Of the single-pill combinations currently available, EFV–TDF–FTC is recommended in guidelines from the U.S. Department of Health and Human Services (DHHS),\(^{19}\) the International Antiviral Society–USA,\(^{45}\) and the British HIV Association.\(^{81}\) The WHO recommends EFV–TDF–FTC or EFV–TDF–3TC, formulated as a single-pill combination, as first-line agents.\(^{54}\) EVG–cobicistat–TDF–FTC is recommended for previously untreated patients in the DHHS and British guidelines.\(^{19,81}\) RPV–TDF–FTC is recommended by the DHHS only for patients with pretherapy HIV-1 RNA levels of less than 100,000 copies per milliliter and CD4+ T-cell counts of more than 200 per cubic millimeter.\(^{19}\) The European AIDS Clinical Society recommends the following single-pill combination regimens: EFV–TDF–FTC, EVG–cobicistat–TDF–FTC, and, if the HIV-1 RNA level is less than 100,000 copies per milliliter, RPV–TDF–FTC.\(^{82}\) The use of fixed-dose combinations was listed as an adherence-boosting strategy (level of evidence, IIIIB)\(^{83}\) in a statement by an International Association of Physicians in AIDS Care panel.\(^{84}\) However, the panel called for future research comparing single-pill combinations with their individual drug components, including analyses of cost.

**References**


**Recommendations**

The first step in evaluating the patient described in the vignette would be to check the HIV-1 genotype to determine whether prior inconsistent use of ART has selected for drug resistance. If not, a single-pill combination is an attractive option owing to the low pill burden and the patient’s stated preference. TDF–FTC, the only NRTI backbone in currently available single-pill combinations, would be reasonable for this patient, given his normal renal function. Although a regimen containing a protease inhibitor as the anchor is sometimes selected if adherence is uncertain, the patient indicates that he is more likely to adhere to a single-pill combination. Each of the anchor drugs in currently available single-pill combinations would be suitable because of his normal renal function and relatively low HIV-1 RNA level and because he is not taking other medications. The selection of a regimen should be based on potential side effects, food requirements, dosing schedule, and, possibly, anticipated adherence; cost may also be a consideration. Regardless of which regimen is chosen, careful clinical, virologic, and immunologic monitoring, along with regular adherence assessment and counseling, will be key contributors to treatment success.

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